Journal of the American Heart Association

VIEWPOINTS

Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect?

Rami Sommerstein, MD; Michael M. Kochen, MD, PhD, MPH; Franz H. Messerli, MD; Christoph Gräni, MD, PhD

Coronavirus disease 2019 (COVID-19) is a pandemic viral disease with its origin in Wuhan, China, in December 2019.[1] As of March 20, 2020, 244 602 patients have tested positive worldwide; and 10 031 (4.1%) of these patients were reported to be deceased because of COVID-19.[2] According to the Chinese Center for Disease Control and Prevention, as of February 11, 2020 with 44 672 confirmed patients, several comorbidities, including cardiovascular diseases and diabetes mellitus, seem to be involved in COVID-19 patients with a severe course.[3] In this largest analysis, 10.5% of fatal cases occurred in patients with cardiovascular disease and 6% in patients with arterial hypertension.[3] It is unclear whether these comorbidities contribute to the higher risk.

See Article by Guo et al.

Most patients with cardiovascular comorbidities qualify for angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy.[4] Of note, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the receptor angiotensin-converting enzyme (ACE) 2 for entry into target cells.[5] Ferrario et al reported that both ACEI and ARB could significantly increase mRNA expression of cardiac ACE2.[6] On the basis of these thoughts, we recently generated the hypothesis that these drugs might play a role in the severe course of COVID-19 cases.[7] More importantly, no clinical-epidemiological data have been put forward and it is unknown whether the hypothesized mechanism plays a pivotal role in COVID-19.

The lay press picked up the theory, causing concern and even anxiety among patients and their healthcare providers. Because of the lack of current evidence of a potential negative impact of these medications on COVID-19, we currently support the position statement of the European and American Societies of Cardiology, who express that ACEIs and ARBs are safe and should be continued and prescribed according to established guidelines.[8,9]

HIGH MORTALITY IN COVID-19: CAUSED BY PRE-EXISTING CARDIOVASCULAR DISEASE, ACEI/ARBS MEDICATION, OR BOTH?

A recently published single-center study on 99 hospitalized patients in China showed that 40% of the cohort had cardiovascular or cerebrovascular disease and 12% had diabetes mellitus.[10] In another Chinese

Key Words: ACE2 ■ angiotensin-converting enzyme inhibitor ■ angiotensin II receptor blocker ■ coronavirus disease 2019 ■ epidemiology ■ infectious diseases

Correspondence to: Rami Sommerstein, MD, Department of Infectious Diseases, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland. E-mail: rami.sommerstein@insel.ch

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JAHA is available at: www.ahajournals.org/journal/jaha

Table. Overview of Current Studies With Adjusted COVID-19 Outcome Analysis for Cardiovascular Risk Factors

Article	Study Population	Cardiovascular Risk Factor	Association of Risk Factor With Fatal Outcome	Adjusted Association With Fatal Outcome	Adjusted for	Comment
Zhou et al, *Lancet*[12]	n=191	Coronary heart disease	2/137 (Survivor) vs 13/54 (non-survivor), OR 21.4 (95% CI, 4.6–98.8, *P*<0.001	OR, 2.14 (95% CI, 0.26–17.8; *P*=0.48)	Lymphocyte count, d-dimer, Sequential Organ Failure Assessment (SOFA) score, age	Sample size too small for meaningful adjustment
Caramelo et al, *medRxiv*[13]	Simulation, based on Chinese Center for Disease Control and Prevention (CCDC) report[3]	Hypertension	Not available	OR, 7.41 (95% CI, 6.33–8.80)	Age, sex	Results obtained by Monte-Carlo simulation, not peer reviewed

ccdc indicates Chinese Center for Disease Control and Prevention; COVID-19 indicates coronavirus disease 2019; sofa: Sequential Organ Failure Assessment; and OR, odds ratio.

report from 138 hospitalized COVID-19 patients, 31% had hypertension, 10% had diabetes mellitus, and 14.5% had cardiovascular disease, being the 3 most common comorbidities.[11] In the latter study, 36 of the 138 patients needed intensive care unit stays, and 58.3% of all intensive care unit patients were reported to have hypertension and 22.1% were reported to have diabetes mellitus.

Beyond these studies, Zhou et al have recently published a study on the risk factors for adult inpatients who die from COVID-19.[12] Notably, of 58 patients with arterial hypertension, 26 (45%) died. This number was significantly higher than the 54 of 191 (28%) from the entire case series. Even more impressive was the fact that 13 of 15 (87%) of the patients with coronary heart disease died, as well as 17 of 36 (47%) with diabetes mellitus.[12] Unfortunately, in our opinion, no studies have been published to date that make an adequate adjustment of cardiovascular risk factors for important covariates. An overview of previous data with adjustment is shown in the Table.

According to the latest analysis of the National Health and Nutrition Examination Survey ACEIs/ARBs are the most prevalent antihypertensive medication among all drug classes.[14] Unfortunately, the European Centre for Disease Prevention and Control does not record any previous drugs in its data collection on COVID-19 patients.[15] Until now, no data are available about the association between previous drug intake and severity of COVID-19 pulmonary outcome. This brings up 4 key questions:

1. Are these cardiovascular comorbidities simply confounders (as they occur frequently with higher age and have been shown to predispose to worse outcome with influenza type A H1N1 infection)?
2. Is there is a link between the comorbidities and SARS-CoV-2 (ie, are patients with heart failure at a higher risk of pulmonary outcome)?
3. Does the comorbidities-associated intake of some drug classes improve or worsen infectivity or the course of COVID-19?
4. If, (and this is a big if), renin-angiotensin system blockade emerges in one way or another as a possible mediator, are there difference between ACEIs and ARBs?

In this issue of the *Journal of the American Heart Association* (*JAHA*), Guo et al[16] point out 2 important issues: On the one hand, the possible overregulation of ACE2 leads to an increased risk of infection of the pulmonary (and possibly other) tissues. On the other hand, there is evidence that there exist both cardio protective and pulmonary-protective activity of ACE2. Which is the case?

Several demographic characteristics are associated with increased ACE2 expression, such as older age and male sex.[17,18,19] In animal studies, ACEIs and ARBs have been shown in rodents to increase the expression of ACE2 mRNA in different organs and tissues, including heart, kidney, and the aorta.[9,20,21] In a study with healthy humans treated with ACEIs and controls, the mean duodenal mRNA expression level of ACE2 was increased 1.9-fold when compared with nontreated controls. However, no significant differences in expression levels were observed in patients treated with ARBs.[22] Beside age and sex, arterial hypertension and diabetes mellitus may upregulate ACE2.[18,23,24] On the contrary, it seems that once infection and acute respiratory distress syndrome ensue, a downregulation of ACE2 occurs. The counterregulatory enzyme ACE2 that degrades angiotensin II to angiotensin[1–7] has been shown

to be beneficial in acute respiratory distress syndrome when replaced, and may offer a novel treatment option.[25,26] Similarly, in animal studies, ACEIs/ARBs have been shown to upregulate ACE2 activity; thereby, they may possibly be favorable once patients are infected with COVID-19.[6,25]

At present, we cannot rule out that long-term intake of ACEIs and/or ARBs may facilitate SARS-CoV-2 entry and virus replication. Conversely, it is yet unknown whether intake of ACEIs and/or ARBs, when infected, is beneficial with regard to pulmonary outcome. Possibly, we are dealing here with a double-edged sword, depending on the phase of the disease: increased baseline ACE2 expression could potentially increase infectivity and ACEI/ARB use would be an addressable risk factor. Conversely, once infected, downregulation of ACE2 may be the hallmark of COVID-19 progression. Consequently, upregulation by preferentially using renin-angiotensin system blockade and ACE2 replacement in the acute respiratory syndrome phase may turn out to be beneficial.

Regardless of these deliberations, we would like to emphasize that many older patients are on renin-angiotensin system blockade because of latent or manifest left ventricular dysfunction and that discontinuation of these drugs may exacerbate frank heart failure. There is little doubt that heart failure is prone to have an unfavorable effect on pulmonary outcome in the course of COVID-19.

In conclusion, cardiovascular diseases and/or their therapy, by affecting ACE2 levels, may play a pivotal role with regard to infectivity and outcome of COVID-19. Whether treatment or disease induced upregulation of ACE2 influences the course of COVID-19 urgently needs to be determined.

ARTICLE INFORMATION

Affiliations

From the Departments of Infectious Diseases (R.S.) and Cardiology (F.H.M., C.G.), Bern University Hospital, Bern, Switzerland; Institute of Family Medicine, University of Freiburg, Germany (M.M.K.); Jagiellonian University, Krakow, Poland (F.H.M.); and Division of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, New York, NY (F.H.M.).

Disclosures

None.

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